ABSTRACT

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The work carried out during my research tenure has been compiled in the form of athesis entitled **"DESIGN, SYNTHESISAND BIOACTIVITY OF BENZIMIDAZOLE, OXADIAZOLE, THIAZOLIDINONE AND THIAZOLE CONTAINING 1,8-NAPHTHYRIDINES"**is classified into five chapters.

CHAPTER-I: An overview of 1,8-naphthyridines and their biological significance.

This chapter describes the introduction, biological significance, synthesis of 1,8-naphthyridinenucleus (brief-review), objectives and scope of the present research.

CHAPTER-II: Synthesis of heterocyclic hybrids based on 1,8-naphthyridine and benzimidazole/1,3,4-oxadiazole scaffolds and their biological activity.

This chapter describes the synthesis and biological activity of new heterocyclic hybrids of benzimidazole/1,3,4-oxadiazoleswith 1,8-naphthyridine as prime motif (Molecular Hybridization approach).

CHAPTER-III: Synthesis of novel 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-ones and their biological evaluation.

This chapter deals the synthesis of iminothiazolidinone bearing 1,8-naphthyridine (base-free and catalyst-free cyclization) and its arylidene derivatives (Knoevenagel condensation). Also describes the antibacterial activity of arylidene derivatives.

CHAPTER-IV: Synthesis of novel *N*-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]acetamide/benzamides and their biological evaluation.

This chapter concern with thesynthesis of new thiazolidinone derivatives bearing 1,8-naphthyridine (base-catalyzed cyclization) and their biological activity.

CHAPTER-V: Synthesis of novel 4-substituted-*N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amines and their biological evaluation.

This chapter states thesynthesis of novel thiazole derivatives possessing 1,8-naphthyridine as primary scaffold (catalyst-free Hantzschthiazole synthesis) and their cytotoxicity evaluation. The significant description of this protocol is simplicity and good yields.

Chemical structures of all the synthesized compounds were characterized on the basis of spectral data such as ^{1}H &^{13}C NMR, IR, mass and elemental analysis.

CHAPTER-I

An overview of 1,8-naphthyridines and their biologicalsignificance

Introduction

Heterocyclic compounds mainly ring comprising nitrogen, oxygen and sulphur atoms have captured the special interest due to their numerous applications in biological aspect.The majority ofcommercially accessible drugs in the market have heterocyclic units in their structures. The development and the chemistry of heterocycles hold a degree of diversity and has become a foremost focus in drug discovery. Over the past few years, a special attention has been focused in gaining insight into the pharmacological applications of molecules involving two or more heterocyclic systems. The incorporation of two different bioactive pharmacophores made into one molecular scaffold is a triumphant and common approach in modern chemistry to explorenovel and very active compounds which may contain synergistic effect on clinical applications.

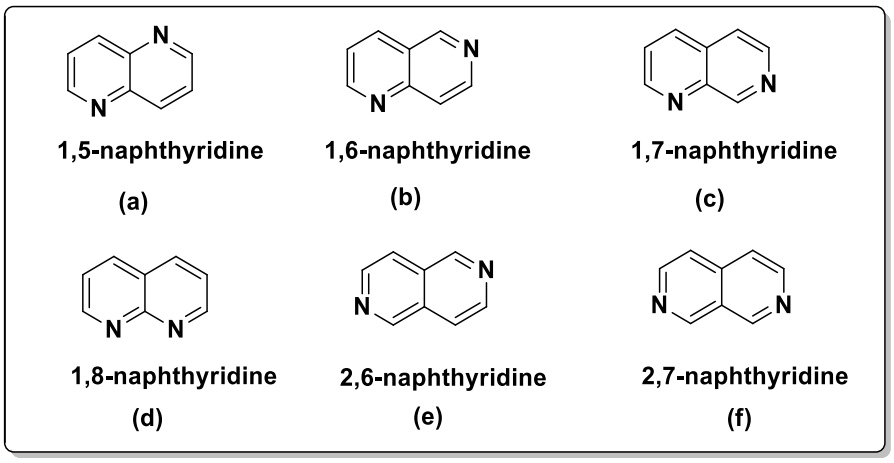


Figure-1: Isomeric naphthyridines

Among the heterocyclics, naphthyridine derivatives have received much attention due to their admirable role in biological, clinical and pharmaceutical applications. Naphthyridinenucleus is made by the fusion of two pyridine rings through two adjacent carbon atoms. They are also called as pyridopyridines or diazanaphthalenes or benzodiazines. However, this system has been indexed in chemical abstracts since

1936 under the headingnaphthyridines. Depending upon the presence of nitrogen atoms in bicyclic system, the available six isomeric naphthyridine(**a-f**) structures are shown in **Figure-1**.

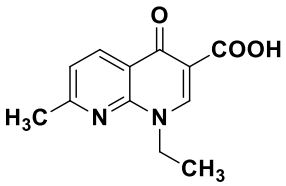
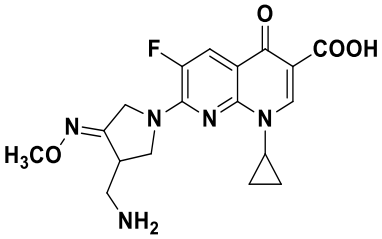
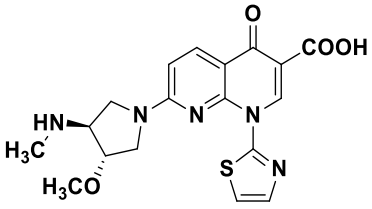
Of the six isomeric naphthyridines (**a-f**), 1,8-naphthyridine (**d**) represents indispensable pharmacophore, and play an important role as pharmaceutical agent (**Table-1**). The paramount importance of these derivatives coupled with earlier interest in this area of research have led us to explore the novel 1,8-naphthyridines.

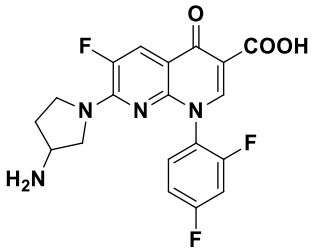
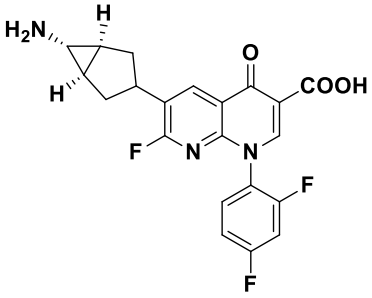
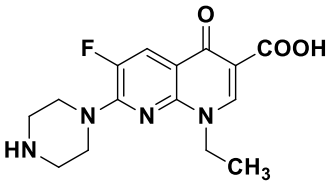
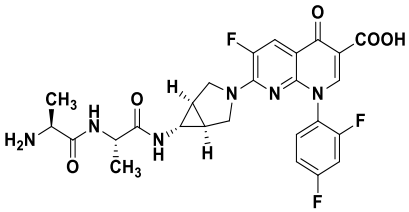
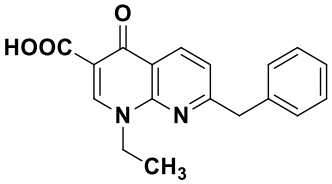
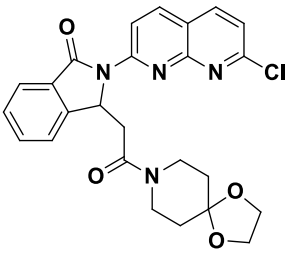
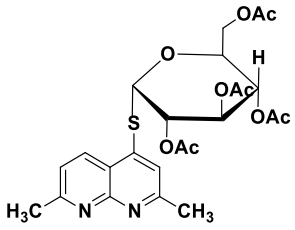
Biological activity:

As early as in 1962, G.Y. Lesher*et al.,* hadidentified the antibacterial activity of 1,8-naphthyridine derivative namely nalidixic acid, which is widely used for the therapy of acute urinary tract infections. This great deal of achievementwas enthused to designing new derivatives possessing 1,8-naphthyridine scaffold across the globe.

Therefore, a sample survey of some 1,8-naphthyridine derivatives associated with biological activities are shown in **Table-1**.

Table-1:Prominent biological applications of 1,8-naphthyridines and their derivatives

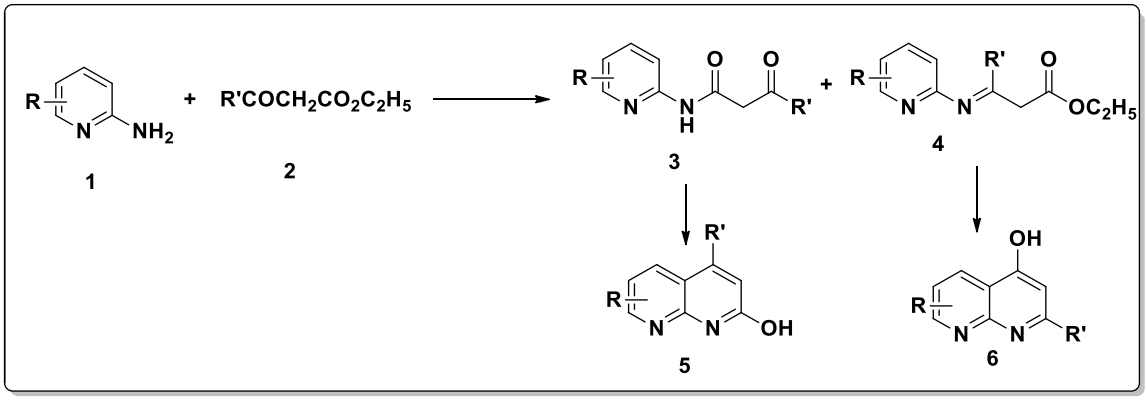
Entry	Compound	Chemical structure	Biological activity
1	Nalidixic acid (ATC code: J01MB02)		Anti-microbial activity
2	Gemifloxacin (ATC code:J0MA15)		Anti-microbial activity
3	Voreloxin/Vosaroxin (ATC Code: L01XX53)		Antitumor

4	Tosulfoxacin (ATC Code: J01MA22)		Antibiotic
5	Trovafloxacin (ATC Code: J01MA13)		Antibiotic
6	Enoxacin (ATC Code: J01MA04)		Antibacterial
7	Alatrofloxacin (HCPPS Code: J0200)		Antibiotic
8	Amfonelic acid (AFA: WIN 25978)		Antibiotic
9	Pazinaclone (DN-2327)		Sedative and Anti-anxiety
10	*N*-β-glycoside derivative of 2,7-dimethyl-1,8-naphthyridine		Cytotoxic activity

Synthesis of 1,8-naphthyridine derivatives:

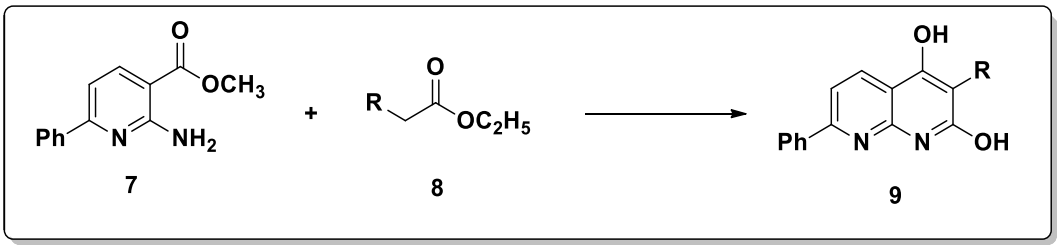
In general, the following major strategies are applied for the construction of1,8-naphthyridine nucleus.

1.2-aminopyridines (**1**) can be converted into an amide (**3**) or anil (**4**) intermediates through condensation by β-ketoesters (**3**)based on the reaction conditions. The cyclization was achieved by the former intermediate (**4**) to furnish corresponding 2-hydroxy-1,8-naphthydrines(**5**) and by the latter intermediate (**10**) to yield the corresponding 4-hydroxy-1,8-naphthydrines (**6**) in good yields (**Scheme-1**).



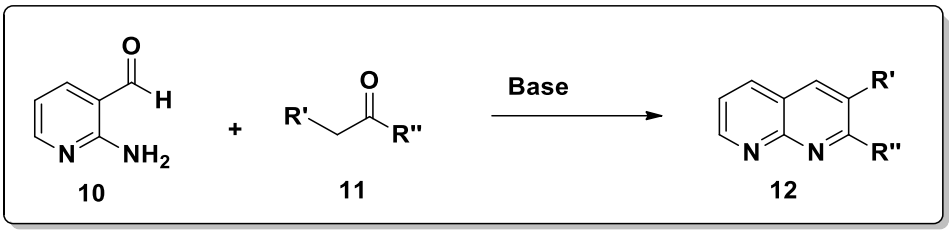
Scheme-1

2.E.M.Hawes and D.G. Wibberley have synthesized 3-substituted-7-phenyl-2,4-dihydroxy-1,8-naphthyridines (**9**) by the reaction of methyl-2-amino-6-phenylnicotinate (**7**) with more reactive esters (**8**)(**Scheme-2)**.



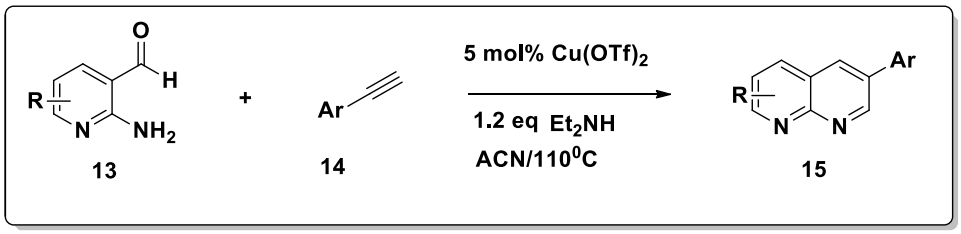
Scheme-2

3.B. Sreenivasulu *et al.*,have developed the synthesis of mono and disubstituted-1,8-naphthyridines (**12**)from the condensation of 2-pyridine-3-carboxaldehyde(**10**) with keto methylene compounds (**11**)in the presence of base(**Scheme-3)**.



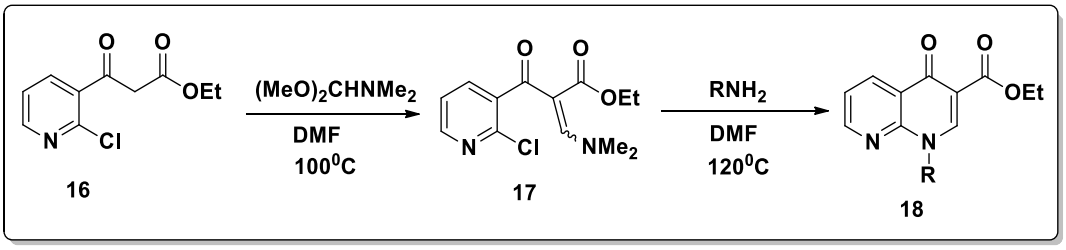
Scheme-3

4. L. Binbin*et al.,* have demonstratedan improvementprotocol for the synthesis of 1,8-naphthyridines (**15**) by the reaction of2-pyridine-3-carboxaldehydes(**13**) with terminal alkynes (**14**) in the presence of copper catalyst and diethylamine in acetonitrile (**Scheme-4)**.



Scheme-4

5.R.A.Bunce and B. Nammalwarhave reported the synthesis of1,4-dihydro-4-oxo-1,8naphthyridine-3-carboxylate esters (**18**) by the reaction of β-ketoester(**16**) with1,1-dimethoxy-*N,N*-dimethylmethanamine in DMFto give β-enaminonederivative (**17**) and then condensed withprimary amines (**Scheme-5)**.



Scheme-5

CHAPTER-II

Synthesis of heterocyclic hybrids based on 1,8-naphthyridine and benzimidazole/1,3,4-oxadiazole scaffolds and their biological activity

Introduction

Interestingly, the 1,8-naphthyridine, benzimidazole, and 1,3,4-oxadiazole scaffolds are some of the basic skeletons occur in several bioactive molecules and have featured in a number of clinically used drugs (**Figure-2**). In particular, the 1,8-naphthyridine and its derivatives exhibited its efficacyin antibacterial, anticonvulsant, anti-HIV, antioxidant, antihypertensive, anti-inflammatory and antitumor activities. Besides, benzimidazole derivativeshave received a special concern due tothe appearance of a fascinating array of biological significancessuch as antimicrobial, anticancer,analgesicandanti-tubercularactivities.Furthermore,1,3,4-oxadiazole derivativesare also represented as an important class of heterocycleswith multiple applicationssuch as antioxidant, anti-ulcerogenic, antiinflammatory,and CNSdepresantactivities. The amide derivatives have various clinical applications such as anticonvulsant, antifungal, insecticidal, antituberculosis, cytotoxic, antihelmintic,and anti-platelet activity.

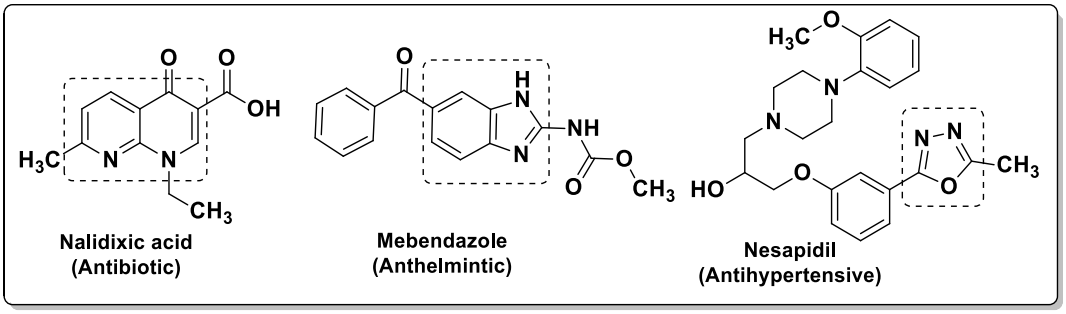
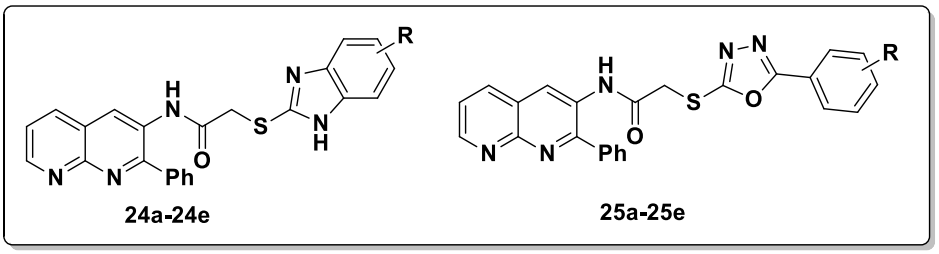


Figure-2: Representative bioactive drugs like naphthyridine, benzimidazole and 1,3,4-oxadiazole analogs

On these considerations and our intense interest for the synthesis of 1,8-naphthyridines possessing multi-structure units, we, herein report a new class of benzimidazoleand/or oxadiazole moieties linked to 1,8-naphthyridine motif.

Present Work

The chemistry of 1,8-naphthyridine and its derivatives was a developing area within the realm of heterocyclicsover the last few decades, because of their synthetic and diverse biological applications. As well, sulphur possessing molecules has been reported to exert attractive clinical applications. It seems of considerable attention to synthesize hybrid molecules of 1,8-naphthyridines via sulphur linkage. Hence in the present work, synthesis of 2-[1*H*-benzo[d]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamides (**24a-24e**) and 2-[(5-aryl-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamides (**25a-25e**)is described and their biological activity has also got.



The synthesis of compounds(**24a-24e** and **25a-25e**)constitutes mainly four stages (**Scheme-6**).

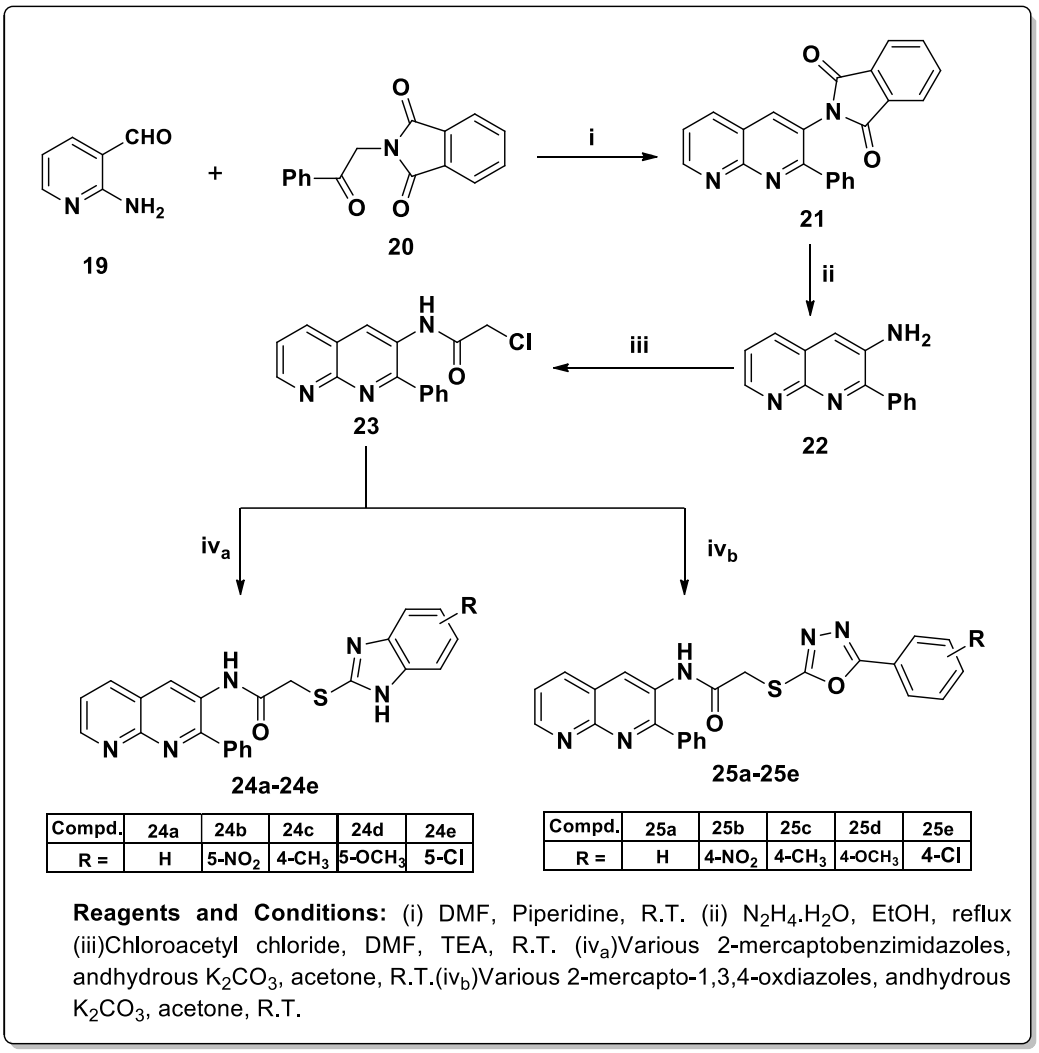
Stage-I:**Synthesis of 2-(2-phenyl-1,8-naphthyridin-3-yl)isoindoline-1,3-dione(21):**
2-aminonicotinaldehyde (**19**) on reaction with 2-(2-oxo-2-phenylethyl)isoindoline-1,3-dione (**20**) in presence of piperidine in DMF afforded the compound (**21**).

Stage-II:**Synthesis of 2-phenyl-1,8-naphthyridin-3-amine** (**22**):
Compound (**21**) upon reaction with hydrazine hydrate yielded the amine (**22**).

Stage-III:**Synthesis of2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (23):**
Stage-III involves a reaction of 2-phenyl-1,8-naphthyridin-3-amine (**22**) with chloroacetylchloroide in the presence of triethylamine to give the compound (**23**).

Stage-IV:**Synthesis of2-[1*H*-benzo[d]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamides (24a-24e) and 2-[5-aryl-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamides (25a-25e):**
In the last stage, compound **(23)** is allowed to react withbenzimidazole-2-thiols in the presence of potassium carbonate and acetone to furnish the products (**24a-24e**),

whereas whenoxadiazole-2-thiols was used in place of benzimidazole-2-thiols under similar conditions, products (**25a-25e**) are formed in appreciable yields.



Compd.	24a	24b	24c	24d	24e
R =	H	5-NO_2	4-CH_3	5-OCH_3	5-Cl

Compd.	25a	25b	25c	25d	25e
R =	H	4-NO_2	4-CH_3	4-OCH_3	4-Cl

Scheme-6: Synthetic protocol for the synthesis of **24a-24e** and **25a-25e**

Antibacterial Activity Evaluation

Antibacterial activity of all the final analogues was screened against the several bacterial strains on comparing with ciprofloxacin drug.

Conclusions

In conclusion, we havesuccessfully synthesized series of 1,8-naphthyridine bearing benzimidazole and/or 1,3,4-oxadiazole derivatives in better yields.It was observed that, most of the titled compounds showed remarkable antibacterial activity.

CHAPTER-III

Synthesis of novel 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-ones and their biological evaluation

Introduction

In recent years, nitrogen and sulfur containing heterocyclic compounds synthesis has emerged as one of the imperativetopic in synthetic chemistry due to their beneficial biological activities**(Figure-4)**. Therefore, manymedicinal chemists have more attention to incorporate the nitrogen and sulphur-architectures on different scaffolds with a view of chemical and biological aspects. Consequently, the combination of assorted bioactive components into one core structure may lead to possess new modes of therapeutic action in drug discovery programme.

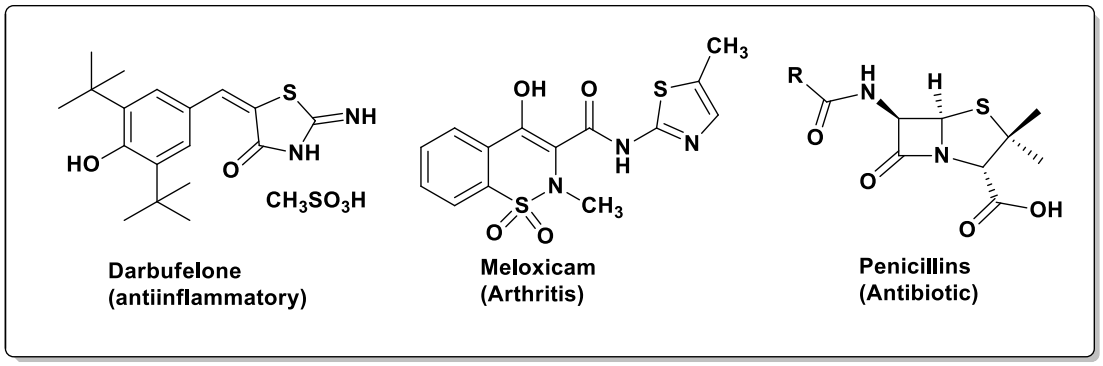
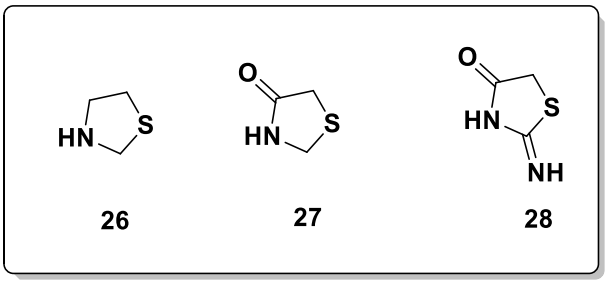


Figure-4: Chemical structures of biologically active compounds

Among the different classes of heterocyclic compounds, 1,8-naphthyridine derivatives have extensive range of pharmacological actionsand can potentially be used to exhibitantibacterial,antiviral,antimycobacterial, anticancer, antihypertensive, and antiplatelet activities.Moreover, 1,3-thiazolidin-4-one (**27**) is a prevalent and most investigated class of five-membered heterocyclic ring system, which is the derivative of thiazolidine (**26**)with a carbonyl function at position-4. Also, 2-imino-1,3-thiazolidin-4-one (**28**) is another important nuclei of thiazolidin-4-one (**27**) series.Thiazolidin-4-one and its 5-arylidene derivatives have been reported to a wide range of medical applicationslikeanti-HIV, antihistaminic, antimicrobial, anti-inflammatory, CNS depressant, anticancer, analgesic/antiinflammatory,

cyclooxygenase inhibitor, antitumor, hypnotic antituberculosis, anti-ischemic, aldose reductase inhibitor/antioxidant, antiproliferative,antidegenerative, and SHP-2 inhibitory activity. Accordingly, our efforts focused towards to the synthesis of a new class of structurally novel 2-imino-thiazolidin-4-one derivatives incorporating on bioactive 1,8-naphthyridine motif.

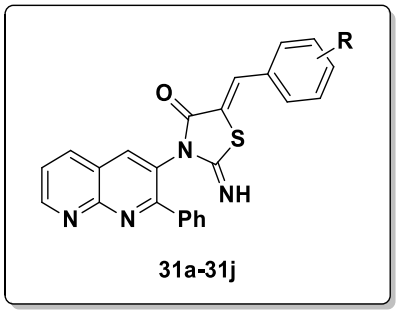


26 27 28

Figure-5

Present Work

It is a known fact that thiazolidin-4-one and 1,8-naphthyridine moieties are considered as 'privileged scaffolds' in heterocycles. This leads to pay an attention to develop the synthesis of a newer series of 1,8-naphthyridine-thiazolidin-4-one derivatives. Hence, in the present chapter, synthesis of 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-ones(**31a-31j**)and their biological activity is described.



31a-31j

Synthesis of the above compounds(**31a-31j**) involves two stages.

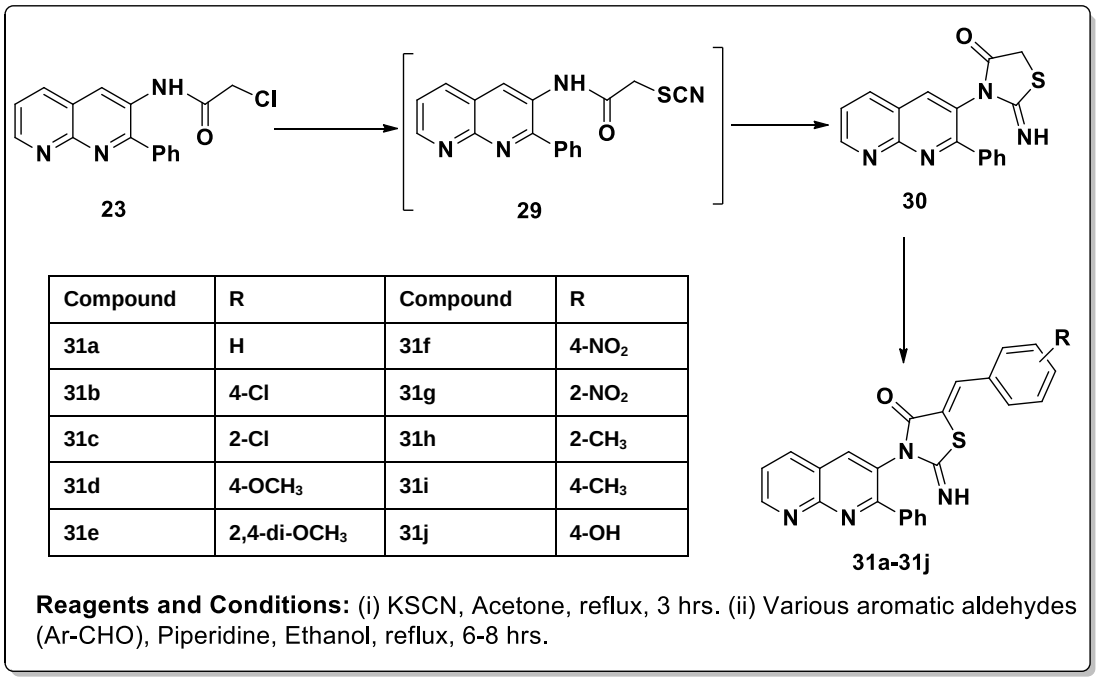
***Stage-I:*Synthesis of2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one (30)**

The compound (**23**) was allowed to react with potassium thiocyanate in acetone to yield 2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one **(30)**.

***Stage-II:*Synthesis of5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-**

yl)thiazolidin-4-ones (31a-31j)

Compound**(30)** was reacted with various arylaldehydes in the presence few drops of ofpiperidine in ethanol to furnish the corresponding arylidene derivatives **(31a-31j)**.



Compound	R	Compound	R
31a	H	31f	4-NO_2
31b	4-Cl	31g	2-NO_2
31c	2-Cl	31h	2-CH_3
31d	4-OCH_3	31i	4-CH_3
31e	2,4-di-OCH_3	31j	4-OH

Reagents and Conditions: (i) KSCN, Acetone, reflux, 3 hrs. (ii) Various aromatic aldehydes (Ar-CHO), Piperidine, Ethanol, reflux, 6-8 hrs.

Scheme-7: Synthetic protocol for the synthesis of titled compounds**31a-31j**

Antibacterial Activity Evaluation

The condensed derivatives (**31a-31j**) were screened for antibacterial activity against the several bacterial strains as compared withciprofloxacin as reference drug.The preliminary results of bioassay demonstrated that the tested compounds exhibited significant antibacterial activity.

Conclusions

In conclusion, we have successfully described a suitable and proficient protocol for the synthesis of 5-arylidene-2-imino-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-4-one derivatives (**31a-31j**) in good yields and also describedtheir antibacterial activity.

CHAPTER-IV

Synthesis of novel *N*-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]acetamide/benzamides and their biological evaluation

Introduction

Over the decades, a large number of organo-sulphur compounds have successfully administered for the treatment of various diseases (**Figure-7**) and they found in several natural and synthetic products.

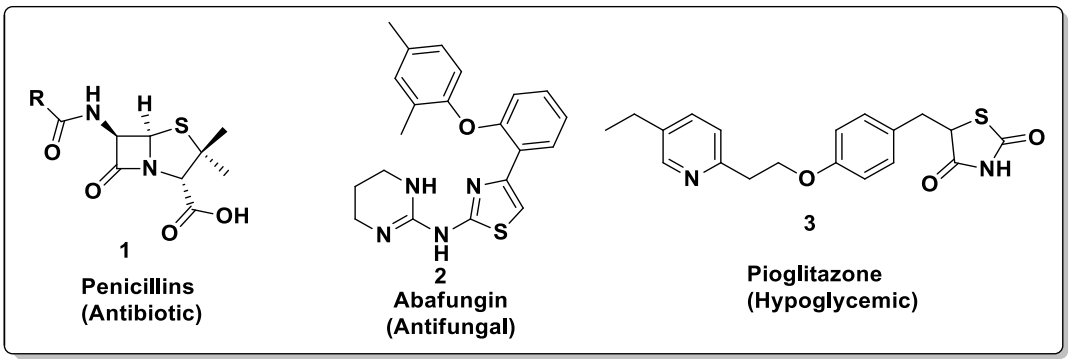


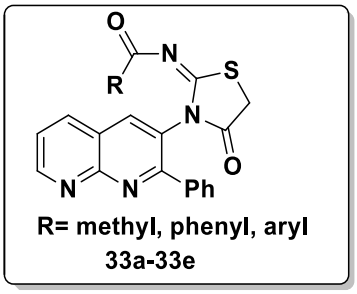
Figure-7: Selected bioactive organo-sulphur drugs

The 1,8-naphthyridine scaffold is a centre of attention in all the nitrogen containing heterocycles due to their biological importance. For instance,they have been reported such as antibacterial, antifungal and antitumor, antihypertensive, HIV-1 integrase mutant, antiplatelet, antidepressant, DNA stabilizing, anti-allergic activities. Besides,4-thiazolidinone is a privileged moiety in five-membered heterocyclic system having diverse medicinal applications. There are some importantdrugs bearing thiazolidin-4-one ring in their structures, such as Thiazolidomycin (antifungal), Etozoline (loop diuretic) and Ralitoline (anticonvulsant). A variety of 4-thiazolidinoneshaving different substituents around the core nucleus are extensively reportedasantibiofilm, $S1P_1$ receptor agonist, antithrombotic, antibacterial, anticanceractivities. They have also been studiedan interesting bioactivities like anti-HIV-1, antiproliferative, anti-tubercular, antioxidant, antihypolipidaemic activities.Inspired by the above considerations, current efforts are focused to developing the biologically potent molecules that embodied with two known bioactive heterocyclic scaffold such as 1,8-

naphthyridine and thiazolidin-4-one in a single frame and their antibacterial activity is evaluated.

Present Work

Encouraged by the diverse applications of 1,8-naphthyridine and thiazolidin-4-onesin the field of pharmaceuticals,an effort has been made for combining valuable effects of these two moieties. Therefore, we report herein the synthesis and antibacterial activity of novel *N*-(4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene)acetamide and *N*-(4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene)benzamides (**33a-33e**).



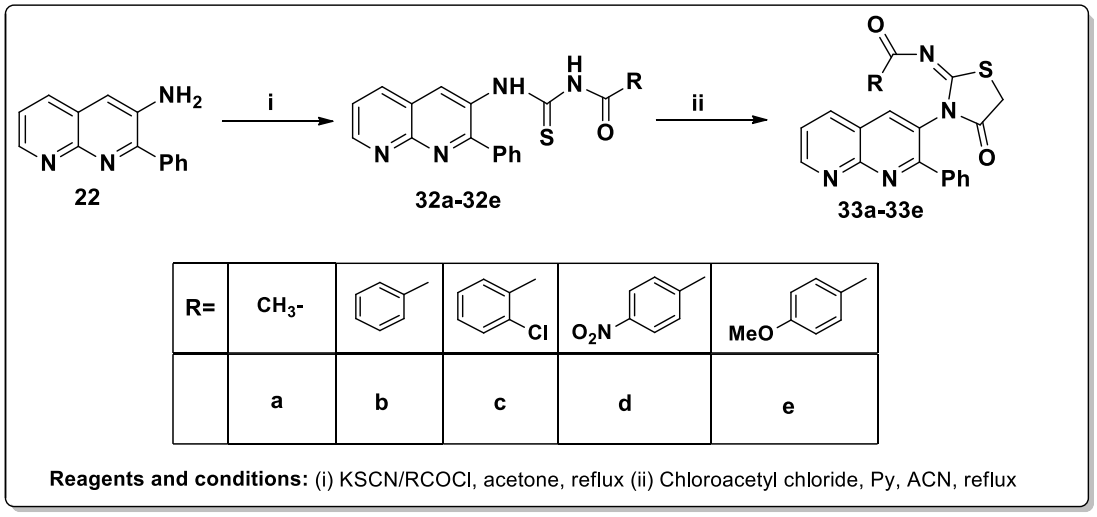
Synthesis of final compounds (**33a-33e**) involves two-steps (**Scheme-8**)

Step-I:**Synthesis of*****N*****-[(2-phenyl-1,8-naphthyridin-3-yl)carbamothioyl]acetamideand substituted *N*-[(2-phenyl-1,8-naphthyridin-3-yl)carbamothioyl]benzamides(32a-32e):**

Compounds (**32a-32e**)were obtained from the reaction of corresponding acid chlorides with potassium thiocyanate in dry acetone, followed by treatment with 2-phenyl-1,8-naphthyridin-3-amine (**22**).

Step-II:**Synthesis of*****N*****-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]acetamide and *N*-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]benzamides** (**33a-33e**):

Reaction of compound (**32a-32e**)with chloroacetyl chloride and pyridine in refluxing acetonitrile resulted in the formation of title compounds (**33a-33e**) in good yields.



Scheme-8: Synthesis of compounds**33a-33e**

Antibacterial Activity Evaluation

The newly synthesized compounds (**33a-33e**) were screened for antibacterial activity against the several microorganisms.The biological potential results exhibited that most of the titled compounds have showed moderate to excellent potency as comparable to Ampicillin drug.

Conclusions

This study has demonstrated that an efficient and facile synthesis of a series of novel *N*-[(2-phenyl-1,8-naphthyridin-3-yl)carbamothioyl]acetamide and*N*-[(2-phenyl-1,8-naphthyridin-3-yl)carbamothioyl]benzamides(**32a-32e**) and *N*-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]acetamideand*N*-[4-oxo-3-(2-phenyl-1,8-naphthyridin-3-yl)thiazolidin-2-ylidene]benzamides (**33a-33e**). Also, described the antibacterial activity of final compounds (**33a-33e**).

CHAPTER-V

Synthesis of novel 4-substituted-*N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amines and their biological evaluation

Introduction

It is observed that some incurable diseases andadverse drug reactions (ADR) are witnessed across the world and that threatens human health and life. These challenging health problems demand an urgency to develop the new drugs for new modes of therapeutic action with improved safety, efficiency and low-toxicity. The efficient construction of new moleculesand their biological screening is a big theme in synthetic chemistry and its related disciplines due to laborious process of lead discovery and optimization process. Nevertheless, the synthesis of heterocyclic units has become an increased interest in pharmaceutical and medicinal chemistry fields. Among the bioactive molecules, nitrogen and sulphur-containing heterocycles are gained much attention.

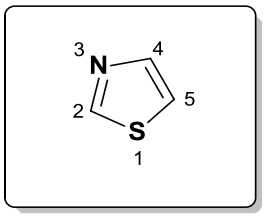


Figure-9: Thiazole molecular structure

Thiazole refers to the class of five-membered heterocylic compound containing both nitrogen and sulphur atoms (**Figure-9**), which shows aromatic character with some dienic nature. Compounds containingthiazole motifs find unique place in therapeutics and known to be associated with immense biological activities such as antidiabetic, antibacterial, anticancer, antimalarial, antifungal, antithyriod and antihistaminic activities. This thiazole nucleus is well known recognizedin a variety of leading drugs like, Ritonavir-antiretroviral, Ravuconazole-antifungal, Sulphathiazole-antimicrobial, Nizatidine-peptic ulcer, Meloxicam-anti-inflammatory (NSAID), Dasatinib-chronic myelogenous leukaemia (CML). In view of the above facts, merging of these twobioactive components (thiazoleand 1,8-naphthyridine) into one system (**Figure-10**) have been reported in the literature to exhibit a wide scope of various biological activities such as antitumor, antibacterial, antipsychotic activities.

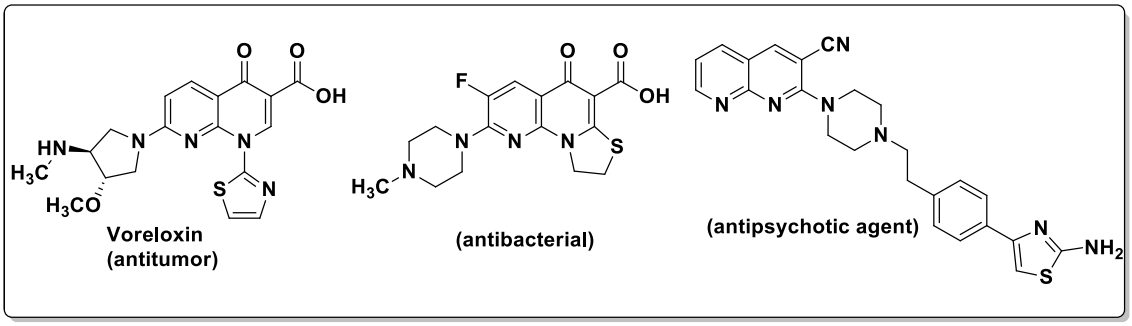
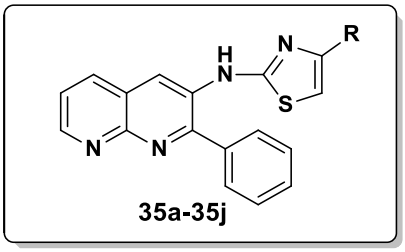


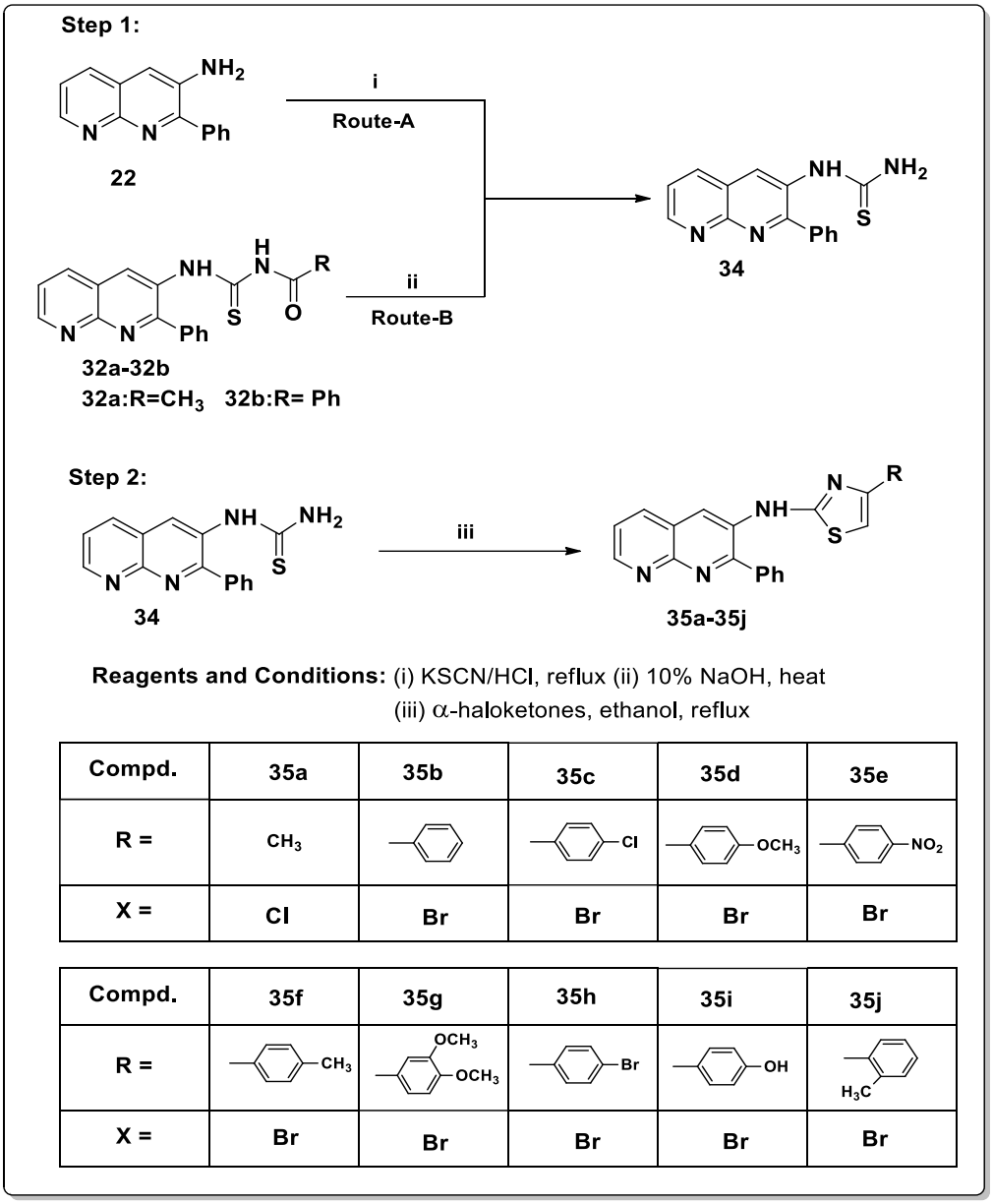
Figure-10: Chemical structures of thiazole bearing 1,8-naphthyridines

In this spirit and in continuation of our efforts directed towards the design and synthesis of thiazole-2-amines with 1,8-naphthyridine as a backbone. Additionally, our objective is also study the cytotoxic activity of the synthesized compounds.

Present Work

The recent literature survey revealed that the synthesis and bioactivity of 1,8-naphthrydine with thiazole moiety are relatively not much explored area. In this context, we attempts to made for the synthesis of 1,8-naphthyridine based thiazol-2-amine derivatives (**56a**–**56j**) with a view of medical importance and their ease of formation.Hantzsch synthesis was utilized for the synthesis of final compounds (**35a**–**35j**) in the present protocol.





Compd.	35a	35b	35c	35d	35e
R =	CH_3				
X =	Cl	Br	Br	Br	Br

Compd.	35f	35g	35h	35i	35j
R =					
X =	Br	Br	Br	Br	Br

Scheme-9: Synthesis of 4-substituted *N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amines

Synthesis of 4-substituted-*N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amine derivatives (**35a**–**35j**) involves two steps (**Scheme-9**).

***Step-I:*Synthesis of 1-(2-phenyl-1,8-naphthyridin-3-yl)thiourea (34):**

Compound(**34**) is the key starting material for the synthesis of targeted molecules and got synthesized by two ways.

In the first route, 2-phenyl-1,8-naphthyridin-3-amine (**22**)was allowed to react with potassium thiocyanate in the presence of diluted HCl to afford compound (**34**).

In the second route, *N*-[(2-phenyl-1,8-naphthyridin-3-yl)carbamothioyl]acetamideand/or benzamide (**32a** or **32b**) underwent hydrolysis with aqueous sodium hydroxide to afford compound thiourea(**34**).

***Step-II:*Synthesis of 4-substituted-*N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amine derivatives** (**35a**–**35j**):

A mixture of thiourea (**34**) and α-haloketones was heated to reflux in ethanol to furnish the title compounds (**35a-35j**) in good yields (76-85%).

Cytotoxic Activity

Most of the thiazole-2-amine derivatives were evaluated for their cytotoxic activity against breast carcinoma cell line (MCF-7) using MTT essay. The preliminary evaluationresults of MTT assay revealed that some of the compounds showed potent cytotoxic effectas compared to the standard drug doxorubicin.

Conclusions

In conclusion, a novel series of 4-substituted *N*-(2-phenyl-1,8-naphthyridin-3-yl)thiazol-2-amines (**35a–35j**) were synthesized and characterized as anticancer agents.